General

Guideline Title

Guidelines for the management of severe traumatic brain injury, 4th edition.

Bibliographic Source(s)

Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the management of severe traumatic brain injury, 4th edition. Campbell (CA): Brain Trauma Foundation; 2016 Sep. 244 p. [341 references]

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24(Suppl 1):S7-S95.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Quality of the body of evidence ratings (High, Moderate, Low, and Insufficient) and levels of recommendation (Level 1, Level IIA, Level IIB, and Level III) are defined at the end of the "Major Recommendations" field.

Evidence Synthesis and Recommendations, Part I: Treatments

Decompressive Craniectomy*

Level I

There was insufficient evidence to support a Level I recommendation for this topic.

Level II A

Bifrontal decompressive craniectomy (DC) is not recommended to improve outcomes as measured by the Glasgow Outcome Scale–Extended (GOS-E) score at 6 months post-injury in severe traumatic brain injury (TBI) patients with diffuse injury (without mass lesions), and with intracranial pressure

(ICP) elevation to values >20 mm Hg for more than 15 minutes within a 1-hour period that are refractory to first-tier therapies. However, this procedure has been demonstrated to reduce ICP and to minimize days in the intensive care unit (ICU).

A large frontotemporoparietal DC (not less than 12 x 15 cm or 15 cm diameter) is recommended over a small frontotemporoparietal DC for reduced mortality and improved neurologic outcomes in patients with severe TBI.

*The committee is aware that the results of the RESCUEicp trial may be released soon after the publication of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. The committee intends to update these recommendations after the results are published if needed. Updates will be available at https://braintrauma.org/coma/guidelines.

Prophylactic Hypothermia

Level I and II A

There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

Early (within 2.5 hours), short-term (48 hours post-injury) prophylactic hypothermia is not recommended to improve outcomes in patients with diffuse injury.

Hyperosmolar Therapy

Level I, II, and III

Although hyperosmolar therapy may lower intracranial pressure, there was insufficient evidence about effects on clinical outcomes to support a specific recommendation, or to support use of any specific hyperosmolar agent, for patients with severe traumatic brain injury.

Cerebrospinal Fluid Drainage

Level I and II

There was insufficient evidence to support a Level I or II recommendation for this topic.

Level III

An external ventricular drainage (EVD) system zeroed at the midbrain with continuous drainage of cerebrospinal fluid (CSF) may be considered to lower ICP burden more effectively than intermittent use.

Use of CSF drainage to lower ICP in patients with an initial Glasgow Coma Scale (GCS) <6 during the first 12 hours after injury may be considered.

Ventilation Therapies

Level I and II A

There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

Prolonged prophylactic hyperventilation with partial pressure of carbon dioxide in arterial blood ($PaCO_2$) of 25 mm Hg or less is not recommended.

Anesthetics, Analgesics, and Sedatives

Level I and II A

There was insufficient evidence to support a Level I or Level IIA recommendation for this topic.

Level II B

Administration of barbiturates to induce burst suppression measured by electroencephalogram (EEG) as prophylaxis against the development of intracranial hypertension is not recommended.
High-dose barbiturate administration is recommended to control elevated ICP refractory to maximum standard medical and surgical treatment. Hemodynamic stability is essential before and during barbiturate therapy.
Although propofol is recommended for the control of ICP, it is not recommended for improvement in mortality or 6-month outcomes. Caution is required as high-dose propofol can produce significant morbidity (U.S. Food and Drug Administration, 2008; Kang, 2002).

Steroids

Level I

The use of steroids is not recommended for improving outcome or reducing ICP. In patients with severe TBI, high-dose methylprednisolone was associated with increased mortality and is contraindicated.

Nutrition

Level I

There was insufficient evidence to support a Level I recommendation for this topic.

Level II A

Feeding patients to attain basal caloric replacement at least by the fifth day and, at most, by the seventh day post-injury is recommended to decrease mortality.

Level II B

Transgastric jejunal feeding is recommended to reduce the incidence of ventilator-associated pneumonia.

Infection Prophylaxis

Level I

There was insufficient evidence to support a Level I recommendation for this topic.

Level II A

Early tracheostomy is recommended to reduce mechanical ventilation days when the overall benefit is felt to outweigh the complications associated with such a procedure. However, there is no evidence that early tracheostomy reduces mortality or the rate of nosocomial pneumonia.
The use of povidone-iodine (PI) oral care is not recommended to reduce ventilator-associated pneumonia and may cause an increased risk of acute respiratory distress syndrome.

Level III

Antimicrobial-impregnated catheters may be considered to prevent catheter-related infections during EVD.

Deep Vein Thrombosis Prophylaxis

Level I and II

There was insufficient evidence to support a Level I or II recommendation for treatment of deep vein thrombosis (DVT) in severe TBI patients.

Level III

Low molecular weight heparin (LMWH) or low-dose unfractionated heparin may be used in

combination with mechanical prophylaxis. However, there is an increased risk for expansion of intracranial hemorrhage.

In addition to compression stockings, pharmacologic prophylaxis may be considered if the brain injury is stable and the benefit is considered to outweigh the risk of increased intracranial hemorrhage. There is insufficient evidence to support recommendations regarding the preferred agent, dose, or timing of pharmacologic prophylaxis for deep vein thrombosis.

Seizure Prophylaxis

Level I

There was insufficient evidence to support a Level I recommendation for this topic.

Level II A

Prophylactic use of phenytoin or valproate is not recommended for preventing late post-traumatic seizures (PTS).
Phenytoin is recommended to decrease the incidence of early PTS (within 7 days of injury), when the overall benefit is felt to outweigh the complications associated with such treatment. However, early PTS have not been associated with worse outcomes.

At the present time there is insufficient evidence to recommend levetiracetam over phenytoin regarding efficacy in preventing early post-traumatic seizures and toxicity.

Evidence Synthesis and Recommendations, Part II: Monitoring

Intracranial Pressure Monitoring

Level I and II A

There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

Management of severe TBI patients using information from ICP monitoring is recommended to reduce in-hospital and 2-week post-injury mortality.

Cerebral Perfusion Pressure Monitoring

Level I

There was insufficient evidence to support a Level I recommendation for this topic.

Level II B

Management of severe TBI patients using guidelines-based recommendations for cerebral perfusion pressure (CPP) monitoring is recommended to decrease 2-week mortality.

Advanced Cerebral Monitoring

Level I and II

There was insufficient evidence to support a Level I or II recommendation for this topic.

(Although patients with desaturations identified with advanced cerebral monitoring have poorer outcomes, Level II evidence showed no improvement in outcomes for monitored patients.)

Level III

Jugular bulb monitoring of arteriovenous oxygen content difference ($AVDO_2$), as a source of information for management decisions, may be considered to reduce mortality and improve outcomes

at 3 and 6 months post-injury.

Evidence Synthesis and Recommendations, Part III: Thresholds

Blood Pressure Thresholds

Level I and II

There was insufficient evidence to support a Level I or II recommendation for this topic.

Level III

Maintaining systolic blood pressure (SBP) at ≥100 mm Hg for patients 50 to 69 years old or at ≥110 mm Hg or above for patients 15 to 49 or over 70 years old may be considered to decrease mortality and improve outcomes.

Intracranial Pressure Thresholds*

Level I and II A

There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

Treating ICP above 22 mm Hg is recommended because values above this level are associated with increased mortality.

Level III

A combination of ICP values and clinical and brain computed tomography (CT) findings may be used to make management decisions.

*The committee is aware that the results of the RESCUEicp trial may be released soon after the publication of these Guidelines. The results of this trial may affect these recommendations and may need to be considered by treating physicians and other users of these Guidelines. The committee intends to update these recommendations after the results are published if needed. Updates will be available at https://braintrauma.org/coma/guidelines.

Cerebral Perfusion Pressure Thresholds

Level I and II A

There was insufficient evidence to support a Level I or II A recommendation for this topic.

Level II B

The recommended target cerebral perfusion pressure (CPP) value for survival and favorable outcomes is between 60 and 70 mm Hg. Whether 60 or 70 mm Hg is the minimum optimal CPP threshold is unclear and may depend upon the patient's autoregulatory status.

Level III

Avoiding aggressive attempts to maintain CPP above 70 mm Hg with fluids and pressors may be considered because of the risk of adult respiratory failure.

Advanced Cerebral Monitoring Thresholds

Level I and II

There was insufficient evidence to support a Level I or II recommendation for this topic.

Level III

Jugular venous saturation of <50% may be a threshold to avoid in order to reduce mortality and improve outcomes.

Definitions

Quality of the Body of Evidence Ratings

High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.
Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient— Evidence is unavailable or does not permit a conclusion.

Level of Recommendation

The levels were *primarily* based on the quality of the body of evidence as follows:

Level I recommendations were based on a high-quality body of evidence.
Level II A recommendations were based on a moderate-quality body of evidence.
Level II B and III recommendations were based on a low-quality body of evidence.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Severe traumatic brain injury (TBI)

Guideline Category

Management

Treatment

Clinical Specialty

Anesthesiology

Critical Care

Emergency Medicine

Internal Medicine

Neurological Surgery

Neurology

Intended Users

Physicians

Guideline Objective(s)

- To address treatment interventions, monitoring, and treatment thresholds that are specific to trauma brain injury (TBI) or that address a risk that is greater in patients with TBI
- To identify key questions, review the literature for evidence, assess and assimilate the evidence, derive recommendations, identify research gaps, and deliver the information to the brain trauma community for integration into its various activities and environments
- To synthesize the available evidence and translate it into recommendations

Target Population

Adults with severe traumatic brain injury (Glasgow Coma Scale score 3-8)

Interventions and Practices Considered

Treatments

- Decompressive craniectomy
- Prophylactic hypothermia
- Hyperosmolar therapy
- Cerebrospinal fluid drainage
- Ventilation therapies
- Anesthetics, analgesics, and sedatives
- Steroids
- Nutrition
- Infection prophylaxis
- Deep vein thrombosis prophylaxis
- Seizure prophylaxis

Monitoring

- Intracranial pressure
- Cerebral perfusion pressure
- Advanced cerebral monitoring

Establishing thresholds

- Blood pressure
- Intracranial pressure
- Cerebral perfusion pressure
- Advanced cerebral monitoring

Note: Not all of the above interventions/practices are recommended in the management of severe traumatic brain injury. Please see the "Major Recommendations" field for context.

Major Outcomes Considered

- Neurological function/changes in Glasgow Outcome Scale (GOS) or Functional Independence Measure (FIM) score
- 2-week, 28-day, 6-month, and 12-month mortality rate
- In-hospital and intensive care unit (ICU) mortality
- Changes in intracranial pressure (ICP) and cerebral perfusion pressure (CPP) values
- Survival rates
- Incidence of pneumonia and other infections
- Incidence of seizures
- Treatment-related adverse effects
- Length of hospital and ICU stay
- Optimal threshold values for blood pressure (BP), ICP, CPP, and advanced cerebral monitoring (ACM)

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Literature Search Strategies

The research librarian from the 3rd Edition reviewed the search strategies for that edition, updated them as needed, and executed the searches for this 4th Edition. For all topics continued from the 3rd Edition, Ovid/MEDLINE was searched from 2006 through July 2013, and an update was performed to include articles published and indexed by the third week of November 2013. For cerebrospinal fluid drainage, the search included literature from 1980 through November 2013. Decompressive craniectomy had previously been included in the surgical guidelines, so the search was conducted as an update from 2001 through November 2013. Relevant studies referred to the guideline authors that were published after the November 2013 update were also included. The search strategies are in Appendix D of the original guideline document.

Abstract and Full-Text Review

Studies were reviewed in a two-step process. The titles and abstracts were reviewed independently by two members of the Methods Team. Articles were retained for full-text review if at least one person considered them relevant based on the abstract. Two Methods Team members read each full-text article and determined whether it met the inclusion criteria (see Appendix E in the original guideline document for inclusion and exclusion criteria). The included and excluded full-text articles for each topic were also reviewed by one or more Clinical Investigators who took the lead on each topic, and full-text articles were available for review by all authors. The key criteria for inclusion were: the study population was adult patients with severe traumatic brain injury (TBI) (defined as Glasgow Coma Scale [GCS] Score of 3 to 8), and the study assessed an included outcome. Differences were resolved via consensus or by a third reviewer. A list of studies excluded after full-text review is in Appendix F in the original guideline document.

Use of Indirect Evidence

Evidence can be defined as indirect when (1) head-to-head comparisons of treatments are not made (e.g., A is compared with placebo and B is compared with placebo but A is not compared with B) or (2) the evidence comes from studies with differences from the pre-specified inclusion criteria, but may be useful in deriving conclusions (e.g., evidence from a study that includes mixed severities or mixed pathologies). This second type of indirect evidence was used in a limited way in these guidelines.

When direct evidence was available, indirect evidence was not used. For most topics, direct evidence was available. However, for some topics in TBI management, no direct evidence was found. In these situations the Methods Team searched for indirect evidence.

When indirect evidence was considered, the Method Team required the same interventions, outcomes, and comparators, but relaxed the criteria related to the population. They considered studies that included patients with moderate as well as severe TBI, mixed ages, or mixed pathologies using the following criteria:

> How relevant to (or different from) our target population is the population in the indirect study?
> To what extent does the relevant physiology of the population in the indirect study approximate the relevant physiology of the population of interest?
> To what extent are differences in physiology expected to influence the outcome?

In what direction would these differences influence the observed effect?

When indirect evidence was included, it is noted in the table describing the quality of the body of evidence in the original guideline document.

Use of Intermediate Outcomes

Direct health outcomes, specifically mortality and neurologic function, are always the priority for the recommendation development. If there were no data about direct health outcomes for a particular topic, the Methods Team considered use of intermediate outcomes if there was evidence to suggest an association between improvement in intermediate outcomes and improvement in direct health outcomes. In this edition, the Methods Team explicitly indicated when an intermediate outcome was the target of a recommendation, and in some cases they qualified the recommendation by stating the treatment was indicated *when the overall benefit was felt to outweigh the complications associated with such treatment*. The Methods Team specified when they included indirect evidence and intermediate outcomes in the assessment of the quality of the body of evidence. (See Quality of the Body of Evidence tables in each topic section in the original guideline document.)

Number of Source Documents

There are 189 publications used for evidence—5 Class 1, 46 Class 2, 136 Class 3 studies, and 2 meta-analyses.

See the "Summary of the Evidence" sections in the original guideline document for detailed information on number and class of included studies for each topic.

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Criteria for Quality Assessment of Individual Studies

Class 1 Evidence is derived from randomized controlled trials (RCTs). However, some may be poorly designed, lack sufficient patient numbers, or suffer from other methodological inadequacies that render them Class 2 or 3.
Class 2 Evidence is derived from cohort studies including prospective, retrospective, and case-control. Comparison of two or more groups must be clearly distinguished. Class 2 evidence may also be derived from flawed RCTs.
Class 3 Evidence is derived from case series, databases or registries, case reports, and expert opinion. Class 3 evidence may also be derived from flawed RCTs, cohort, or case-control studies.

Quality of the Body of Evidence Ratings

High—High confidence that the evidence reflects the true effect. Further research is very unlikely to change the confidence in the estimate of effect.
Moderate—Moderate confidence that the evidence reflects the true effect. Further research may change the confidence in the estimate of effect and may change the estimate.
Low—Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.
Insufficient— Evidence is unavailable or does not permit a conclusion.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Quality Assessment of Individual Studies

All included studies were assessed for potential for bias, which is an approach to assessing the internal validity or quality of the study. This assessment is a core component of systematic review methods. It is an approach to considering and rating studies in terms of how the study design and conduct addressed issues such as selection bias, confounding, and attrition. The criteria used in the 3rd Edition were maintained and applied to the newly identified studies of monitoring and treatments. The criteria for threshold studies were revised to be specific to the structure of studies of thresholds. (See Appendix G in the original guideline document for a complete list of the quality criteria used for individual studies.)

Two reviewers independently evaluated each study using the criteria appropriate for the study design (i.e., randomized controlled trials [RCTs], observational studies, studies of thresholds) and rated the study as Class 1, 2, or 3 evidence based on the combination of study design and quality rating (see the "Rating Scheme for the Strength of the Evidence" field). Class 1 is the highest class and is limited to good-quality randomized trials. Class 2 includes moderate-quality RCTs and good-quality cohort or case-control studies. Class 3 is the lowest class and is given to low-quality RCTs, moderate- to low-quality cohort or case control studies, and case series and other non-comparative designs. Differences in ratings were then reconciled via consensus or the inclusion of a third reviewer as needed.

Data Abstraction

Data were abstracted from studies by a member of the Methods Team and checked for errors by a second member. Information was recorded about the study population, design, and results. For topics on which meta-analysis was considered, the study characteristics and results were independently abstracted by two people and verified by a third.

Key elements of each included study are presented in the Summary of Evidence tables for each topic section in the original guideline document.

Synthesis

The final phase of the evidence review is the synthesis of individual studies into information that the Clinical Investigators and the Methods Team use to develop recommendations. This synthesis is described for each topic in the section titled "Evaluation of the Evidence," following the Recommendations and preceding the "Evidence Summary" (see the original guideline document).

Identification of Subtopics and Synthesis

For each treatment, monitoring, or thresholds topic, the Clinical Investigators identified important subtopics. For example, for Nutrition, there are questions about the route or mode of feeding, the timing of feeding, glycemic control, and supplements. The studies in each topic were reviewed to determine if quantitative synthesis—meta-analysis was feasible. This involved determining if the patient populations, specifics of the intervention, and the outcomes were similar enough that the study results could be combined. The result of this assessment is included in the "Quality of the Body of Evidence" table for each subtopic (see the original guideline document). For this edition, the Methods Team did not identify any topics for which quantitative synthesis was appropriate according to current standards. For this reason, the evidence was synthesized qualitatively.

Quality of the Body of Evidence

Assessing the quality of the body of evidence involves four domains: the aggregate quality of the studies, the consistency of the results, whether the evidence provided is direct or indirect, and the

precision of the evidence. See the "Rating Scheme for the Strength of the Evidence" field for the ratings for the quality of the body of evidence. The criteria are outlined below, and more detailed information is provided in Appendix H in the original guideline document. In addition, the number of studies and number of included subjects are considered. Based on these, an overall assessment is made as to whether the quality of the body of evidence is high, moderate, low, or insufficient. The assessment of the body of evidence for each subtopic is included in a table in each section of the original guideline document.

Criteria

Quality of Individual Studies: This identifies the quality of the individual studies. It details how many are Class 1, Class 2, and Class 3.

Consistency: Consistency is the extent to which the results and conclusions are similar across studies. It is rated High (all are similar), Moderate (most are similar), or Low (no one conclusion is more frequent). It is NA (not applicable) when the body of evidence consists of a single study.

Directness: Directness is defined as whether the study population is the same as the population of interest and if the outcomes are clinical rather than intermediate outcomes. Evidence is labelled as Direct, Indirect, or Mixed.

Precision: Precision is the degree of certainty surrounding the effect estimate for a given outcome. Precision is rated as High, Moderate, or Low. How this is determined depends on the type of analysis used in a specific study but may include consideration of the range of confidence intervals or the significance level of p-values.

These criteria are then considered when assigning a rating to the body of evidence.

A determination of quality of the body of evidence requires a judgment about the relative importance of the criteria, and these may vary across topics and subtopics. The following general examples are provided to illustrate the variations that are possible, but are not intended as exhaustive decision rules. If two or more Class 1 studies demonstrate contradictory findings for a particular topic, the overall quality of the body of evidence may be assessed as low because there is uncertainty about the effect. Similarly, Class 1 or 2 studies that provide indirect evidence may only constitute low-quality evidence overall. In some cases, the body of evidence may be a single study, but the rating may vary. A single study may constitute a high-quality body of evidence if it is a large, multisite, Class 1 RCT; a moderate-quality body of evidence if it is a single-site Class 2 study with a sizable sample and moderate precision; or insufficient evidence if the sample is small and the precision of the estimate of effect is low.

Applicability

Applicability is the extent to which research findings are useful for informing recommendations for a broader population (usually the population that is the target of the recommendations). What is important to consider when assessing applicability will vary depending upon the topic, and the assessment is context-specific. Consequently, there is currently no generally accepted universal rating system for applicability. Common considerations focus on the characteristics of the patient population (e.g., to which patients are the results applicable?) and the settings for care delivery (e.g., where could a similar result be expected?). Even if the patient population meets the inclusion criteria established for the review, there may be specific characteristics that affect applicability. The characteristics of the setting in which a study was conducted may also be important to consider. For example, a study conducted in a Veterans Administration (VA) Medical Center may or may not be applicable to other settings, depending upon how similar the Veterans are to the population of interest, or how similar the context of the VA is to the care setting of interest. Additional characteristics to be considered may include the geographic location (e.g., country, state, urban, or rural) and the type of hospital (e.g., level of trauma center). The geographic area and type of hospital are considered because it is possible that the patients, practice patterns, and available services are different across environments. In this edition, the applicability of individual studies was considered in the Quality of the Body of Evidence and Applicability section immediately following the recommendations.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Scope of the Review

Topic Refinement

Topics for inclusion in this edition were primarily carried forward from the 3rd Edition. Two topics were added (decompressive craniectomy and cerebrospinal fluid drainage), and the questions within topics were revised based on input from the Clinical Investigators. Topics related to good clinical care that are not traumatic brain injury (TBI)-specific were excluded. For example, general procedures for reducing hospital-acquired infections are not included. However, measures designed to prevent ventilator-associated pneumonia (VAP) are included based on data suggesting the rate of VAP is higher for TBI patients than for other critical care patients.

Topics Included in This Edition

The topics are organized in three categories that are specific to severe TBI in adults: treatments, monitoring, and thresholds (see the "Interventions and Practices Considered" and the "Major Recommendations" fields for the list of topics).

Major Changes for This Edition

Major changes for this edition are summarized here, and details are presented in Appendix A of the original guideline document.

Cerebral Fluid Drainage. New topic.
Decompressive Craniectomy. New topic.
Deep Vein Thrombosis. For risks that are traumatic brain injury-specific, direct evidence was not identified. Indirect evidence was identified and included.
Intracranial Pressure Technology. Technology assessment is outside the scope of management guidelines and no longer included.
Hyperventilation. Renamed Ventilation Therapies.
Brain Oxygen Monitoring. Renamed Advanced Cerebral Monitoring.
Infection Prophylaxis. Focus on Ventilator Associated Pneumonia and External Ventricular Drain infections. Indirect evidence was identified and used.
Intracranial Pressure Monitoring, *Cerebral Perfusion Pressure Monitoring, Advanced Cerebral Monitoring*. Divided into (a) benefits and risks of monitoring (Monitoring) and (b) values to be targeted or avoided (Thresholds).

Analytic Frameworks

Analytic frameworks are tools developed to help guide systematic reviews. They show the relationships between the variables specific to each key question within each topic. They identify the relevant populations, interventions, intermediate outcomes, harms, clinical outcomes, and other factors, and they help clarify what is and is not outside the scope of the review. Three analytic frameworks were developed, one each for Treatments, Monitoring, and Thresholds (see Appendix C in the original guideline document). These were used by the Methods Team and the Clinical Investigators to establish the scope of the literature search and to clarify the distinction between studies of treatments, monitoring, and thresholds.

Development of Recommendations

Inclusion of Recommendations

Class 1, 2, or 3 studies constitute the evidence on which the recommendations are based. Under current methods, identification of evidence is necessary but not sufficient for the development of recommendations. No recommendations were made without a basis in evidence.

Once evidence was identified, whether it could be used to inform recommendations was based on the quality of the body of evidence and consideration of applicability. Given this, there were cases in which evidence was identified, but the quality was low and applicability concerns restricted the ability to translate the evidence into recommendations. Even if a recommendation was not made, the evidence was included to serve as a placeholder for future consideration, because in the future, new studies may be added, resulting in changes in the assessment of the quality of the body of evidence.

Level of Recommendation

Recommendations in this edition are designated as Level I, Level II A, Level II B, or Level III. The Level of Recommendation is determined by the assessment of the quality of the body of evidence, rather than the class of the included studies. The levels were *primarily* based on the quality of the body of evidence (see the "Rating Scheme for the Strength of the Recommendations" field).

The Class of studies in the body of evidence was the basis for making a Level II B or III recommendation: Level II B recommendations were based on a body of evidence with Class 2 studies, with direct evidence but of overall low quality, and Level III recommendations were based on Class 3 studies, or on Class 2 studies providing only indirect evidence.

Applicability could result in a Level III recommendation (e.g., a "moderate-quality body of evidence" with significant applicability concerns). In this edition, applicability alone was not used to downgrade a recommendation. However, given the lack of standards and developed methods in this area, The Methods Team cited applicability issues that were identified and discussed by the authors.

"Insufficient" was used in cases in which the body of evidence was insufficient either because there were no studies identified, or because the body of evidence had major quality limitations. If the evidence was insufficient, no recommendations were made.

Recommendation Review and Revision

Preliminary Topic Reviews

After completion of the literature review, identification of new studies, quality assessment, and data abstraction, the Methods Team sent drafts for each topic to two Clinical Investigators. The Clinical Investigators read the included studies and the draft recommendations, provided input, and suggested additional studies for consideration. Methods Team members incorporated the input, acquired and reviewed new studies, and provided the Clinical Investigators with new publications and a revised summary of the evidence for each topic.

Clinical Investigator Review Meeting

In a two-day meeting in 2014, each topic was presented and discussed by the group. Based on these discussions, the Methods Team revised the searches and recommendations.

Review of Complete Draft

The complete draft of all topics as well as the other sections of the guidelines (e.g., Methods, Appendices) was sent to all Clinical Investigators for review and comment. Phone conferences were held to answer questions, discuss the draft, and finalize the document throughout 2015.

Rating Scheme for the Strength of the Recommendations

Level of Recommendation

The levels were *primarily* based on the quality of the body of evidence as follows:

Level I recommendations were based on a high-quality body of evidence.
Level II A recommendations were based on a moderate-quality body of evidence.
Level II B and III recommendations were based on a low-quality body of evidence.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Recommendation Review and Revision

Peer Review

After revisions were made based on input from the Clinical Investigators, the 4th Edition was sent out for peer review. The Peer Review Committee was comprised of topic-specific traumatic brain injury (TBI) clinicians, methodologists, representatives of specialty societies, and related stakeholders. Their input was reviewed and incorporated as appropriate. A comprehensive review was also conducted by members of the American Association of Neurological Surgeons/Congress of Neurological Surgeons Joint Guidelines Committee, in collaboration with the Clinical Investigators and Methods Team.

Evidence Supporting the Recommendations

References Supporting the Recommendations

Kang TM. Propofol infusion syndrome in critically ill patients. Ann Pharmacother. 2002 Sep;36(9):1453-6. PubMed

U.S. Food and Drug Administration (FDA). Diprivan (propofol) injectable emulsion.Silver Spring (MD): U.S. Food and Drug Administration (FDA); 2008 Feb [accessed 2016 Aug 04].

Type of Evidence Supporting the Recommendations

See the individual chapters of the original guideline document (particularly the "Summary of the Evidence" sections) for the type of evidence supporting the recommendations.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- Improved management of severe traumatic brain injury (TBI)

- The Brain Trauma Foundation guidelines have been integrated into the Brain Trauma Evidence-based Consortium (B-TEC). In that context, the guidelines will contribute to, and benefit from, the realization of the mission of B-TEC to cause a paradigm shift in the assessment, diagnosis, treatment, and prognosis of brain trauma.

See the individual chapters of the original guideline document (particularly the "Summary of the Evidence" sections) for discussions of benefits of specific interventions reported in the reviewed studies.

Potential Harms

- Side effects of anesthetics, analgesics, and sedatives include hypotension and decreased cardiac output, as well as increased intrapulmonary shunting, which may lead to hypoxia. These may give rise to a paradoxical decrease in cerebral perfusion pressure, which may negate the benefits of decreased intracranial pressure (ICP). Because of potential toxic side effects, duration and dose of administration also means that the monitoring of sedative doses needs to be diligently observed.
- Propofol infusion syndrome was first identified in children but can occur in adults as well. Common clinical features include hyperkalemia, hepatomegaly, lipemia, metabolic acidosis, myocardial failure, rhabdomyolysis, and renal failure, resulting in death. Thus, extreme caution must be taken when using doses greater than 5 mg/kg/hour, or when usage of any dose exceeds 48 hours in critically ill adults.
- Infection risks such as ventilator associated pneumonias (VAP) and central line-associated bacteremias are increased in all critically ill patients. Patients undergoing ICP monitoring are reported to have related infection rates as high as 27%.

See the individual chapters of the original guideline document (particularly the "Summary of the Evidence" sections) for discussions of harms of specific interventions reported in the reviewed studies.

Contraindications

Contraindications

In patients with moderate or severe traumatic brain injury (TBI), high-dose methylprednisolone is associated with increased mortality and is contraindicated.

Qualifying Statements

Qualifying Statements

- Any opinions, findings and conclusions or recommendations expressed in this material are those of the authors and do not necessarily reflect the views of the U.S. Army Contracting Command, Aberdeen Proving Ground, Natick Contracting Division, Stanford University, or the Brain Trauma Foundation.
- The information contained in the Guidelines for the Management of Severe Traumatic Brain Injury reflects the current state of knowledge at the time of publication. The Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons, and other collaborating organizations are not engaged in rendering professional medical services and assume no responsibility for patient outcomes resulting from application of these general recommendations in specific patient circumstances. Accordingly, the Brain Trauma Foundation, American Association of Neurological Surgeons, and Congress of Neurological Surgeons consider adherence to these clinical practice guidelines will not necessarily assure a successful medical outcome. The information contained in these guidelines reflects published scientific evidence at the time of completion of the

guidelines and cannot anticipate subsequent findings and/or additional evidence, and therefore should not be considered inclusive of all proper procedures and tests or exclusive of other procedures and tests that are reasonably directed to obtaining the same result. Medical advice and decisions are appropriately made only by a competent and licensed physician who must make decisions in light of all the facts and circumstances in each individual and particular case and on the basis of availability of resources and expertise. Guidelines are not intended to supplant physician judgment with respect to particular patients or special clinical situations and are not a substitute for physician-patient consultation. Accordingly, the Brain Trauma Foundation, American Association of Neurological Surgeons, and Congress of Neurological Surgeons consider adherence to these guidelines to be voluntary, with the ultimate determination regarding their application to be made by the physician in light of each patient's individual circumstances.

- The scope and purpose of this work is two-fold: to synthesize the available evidence and to translate it into recommendations. This document provides recommendations only when there is evidence to support them. As such, they do not constitute a complete protocol for clinical use. The authors' intention is that these recommendations be used by others to develop treatment protocols, which necessarily need to incorporate consensus and clinical judgment in areas where current evidence is lacking or insufficient. The authors believe it is important to have *evidence-based* recommendations in order to clarify what aspects of practice currently can and cannot be supported by evidence, to encourage use of evidence-based treatments that exist, and to encourage creativity in treatment and research in areas where evidence does not exist. The communities of neurosurgery and neuro-intensive care have been early pioneers and supporters of evidence-based medicine and plan to continue in this endeavor.
- The guidelines address treatment interventions, monitoring, and treatment thresholds that are particular to traumatic brain injury (TBI) or that address a risk that is higher in TBI patients. The scope of the guidelines is not intended to cover all topics relevant to the care of patients with severe TBI. Topics related to general good care for all patients, or all trauma patients, are not included. In the future, new topics will be added only if they are TBI-specific. Topics included in prior editions that cover general medical care needs by many patients, such as infection and deep vein thrombosis prophylaxis, have been narrowed to focus on TBI-specific risks or issues. As stated, the recommendations are limited to those areas for which an evidence base was identified. Developing protocols that incorporate general best practices for trauma patients (not TBI-specific) and that provide guidance, suggestions, or options in areas of TBI management where the evidence is insufficient is outside the scope of this endeavor.
- Despite improvements in the 4th Edition, the recommendations are limited in many areas, reflecting persisting gaps in the evidence base for severe TBI management. Although there have been numerous new publications in the field since the 3rd Edition of the Guidelines was published in 2007, many repeat the same methodologic flaws found in previous research.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Quick Reference Guides/Physician Guides

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the management of severe traumatic brain injury, 4th edition. Campbell (CA): Brain Trauma Foundation; 2016 Sep. 244 p. [341 references]

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Brain Trauma Foundation - Disease Specific Society

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Management of Severe Traumatic Brain Injury Guidelines Committee

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Guideline Endorser(s)

American Association of Neurological Surgeons - Medical Specialty Society

Congress of Neurological Surgeons - Professional Association

Guideline Status

This is the current release of the guideline.

This guideline updates previous versions: Brain Trauma Foundation, American Association of Neurological Surgeons, Congress of Neurological Surgeons. Guidelines for the management of severe traumatic brain injury. J Neurotrauma. 2007;24(Suppl 1):S7-S95.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Brain Trauma Foundation Web site.

Availability of Companion Documents

The following is available:

Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GW, Bell MJ, Bratton SL, Chesnut R, Harris OA, Kissoon N, Rubiano AM, Shutter L, Tasker RC, Vavilala MS, Wilberger J, Wright DW, Ghajar J. Guidelines for the management of severe traumatic brain injury, 4th edition. Executive summary. Campbell (CA): Brain Trauma Foundation; 2016 Sep. 10 p. Available from the Brain Trauma Foundation Web site.

Patient Resources

None available

NGC Status

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